

REMARKS

Status of the claims:

With the above amendments, claims 1 and 4 have been amended and claims 13-14 have been added. Claims 1-14 are pending with claims 7-12 having been withdrawn from a prior restriction requirement. Thus, claims 1-6 and 13-14 are ready for further action on the merits. No new matter has been added by way of the above amendments. The amendments to claim 1 and new claim 13 have support at page 4, lines 16-18. New claim 14 has support at page 3, line 12. Reconsideration is respectfully requested in light of the following remarks.

Restriction/ Election

The Examiner has required a three-way restriction according to the following groups.

Group I, claims 1-6, drawn to a method of denaturing allergens with salts of calcium or strontium,

Group II, claims 7-9, drawn to a composition containing a calcium or strontium salt, organic acid, or phosphoric acid and water or alcohol,

Group III, claims 10-12, drawn to a composition containing a calcium or strontium salt, water soluble polymer including

PVA, polyacrylic acid/salt, polyethylene glycol or PVP, and water or alcohol.

Applicants confirm the election **without traverse** of Group I, claims 1-6.

Rejections under 35 USC §§102/103

Claims 1 and 2 are rejected under 35 USC §102 (b) as being anticipated by Pluim '239 (US Patent No. 4,594,239).

Claims 1, 2, 4, and 5 are rejected under 35 USC §102 (b) as being anticipated by, or in the alternative, under 35 USC §103(a) as being unpatentable over DE '476 (DE 3525476).

These rejections are traversed for the following reasons.

Disclosure of Pluim '239

Pluim '239 discloses a method for neutralizing urushiol. The technique involves contacting urushiol with a chlorine-containing compound in a liquid medium. The chlorine-containing compound is sodium or calcium hypochlorite in an aqueous solution. In another embodiment in the invention of Pluim '239, the chlorine-containing compound is a chloramine in a liquid organic medium.

Pluim '239 fails to disclose denaturing allergens.

Disclosure of DE '476

DE '476 discloses a filter that is composed of calcium carbonate and/or magnesium carbonate. The filter in DE '476 also contains iron III salts, at least some as a chloride salt. The resulting alkaline earth metal chlorides are hygroscopic and keep the filter moist. As a result, the filter is said to retain solid pollutants such as soot, cancerigenic aromatic compounds (benzopyrene) and lead oxide. Nitrogen oxides of the type NO_x are oxidized by iron III compounds to NO₂ and are bound as nitrates with the release of carbon dioxide. Sulfur dioxide is bound either as sulfite, likewise with release of CO₂, or oxidized by iron III compounds to a sulfate. The iron II compounds formed are oxidized by atmospheric oxygen back to iron III compounds. The reactive substances are introduced into an inert, porous support matrix. Preference is given to cellulose fibers in the form of filter paper.

DE '476 fails to disclose denaturing allergens.

Removal of the Rejections over Pluim '239 and DE '476

Both Pluim '239 and DE '476 fail to disclose or suggest denaturing allergens. Moreover, neither Pluim '239 nor DE '476 disclose or suggest denaturing allergens from mites (as in claim 13) nor do they suggest the use of an acetate, propionate or chloride as claimed in claim 14. Thus, neither Pluim '239 nor

DE '476 anticipates the instant invention because neither Pluim '239 nor DE '476 discloses the elements of the instant invention.

Pluim '239 describes a technique for neutralizing urushiol, which is a 1,2-dihydro 3-(C₁₅₋₁₇alkyl)benzene compound (see column 2, lines 25-29 in Pluim '239). In contrast, the instant invention claims a method of denaturing allergens. Allergens from pollen, animal dander, moulds, and domestic mites (as now recited in instant claim 1) are protein. Please find the attached reference from Clinical and Experimental Allergy, Vol. 27, p. 253 wherein it is explained that allergens are protein in nature. Moreover, a definition of "allergen" can be found in Rikagakujiten (Dictionary of Physics and Chemistry) 3rd edition, published by Iwanami Shoten, wherein it is exemplified as a protein or choline (Please see the English translation). Thus, Pluim '239 cannot anticipate the instant invention because it fails to disclose or suggest the denaturing of allergens (that are protein in nature). Withdrawal of the rejection is warranted and respectfully requested.

DE '476 describes a filter for removing Nox by Fe(III) and the filter can comprise calcium carbonate (column 2, line 15). The filter may remove pollens (see column 2, line 9 in DE '476), but this removal is simply by adsorption. DE '476 does not

disclose or suggest denaturing allergens. Accordingly, DE '476 cannot anticipate the instant invention.

Further, Applicants assert that the Examiner has failed to make out a *prima facie* case of obviousness with regard to the 35 USC §103(a) rejection over DE '476. Three criteria must be met to make out a *prima facie* case of obviousness.

- 1) There must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings.
- 2) There must be a reasonable expectation of success.
- 3) The prior art reference (or references when combined) must teach or suggest all the claim limitations.

See MPEP §2142 and *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991). In particular, the Examiner has failed to meet the third element to make a *prima facie* obviousness rejection. DE '476 does not disclose or suggest denaturing allergens. Accordingly, DE '476 cannot render obvious the instant invention. Withdrawal of the rejection is warranted and respectfully requested.

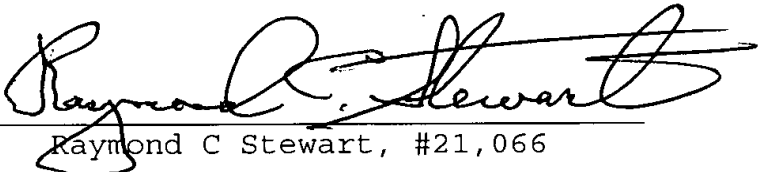
With the above remarks and amendments, it is believed that the claims, as they now stand, define patentable subject matter such that a passage of the instant invention to allowance is warranted. A Notice to that effect is earnestly solicited.

If any questions remain regarding the above matters, please contact Applicant's representative, T. Benjamin Schroeder (Reg. No. 50,990), in the Washington metropolitan area at the phone number listed below.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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Attachments

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

The claims have been amended as follows:

1. (Amended) A method for denaturing allergens originated from mites, hair or epithelium of pets, cockroaches, feathers, fungi and pollens of plants which comprises applying an effective amount of an [the] alkaline earth metal salt selected from calcium and strontium salts to a [the] place where [allergen exists] allergens exist or will exist.

4. (Amended) A method for denaturing allergens according to claim 1, wherein the alkaline earth metal salt is selected from the group consisting of acetate, propionate, nitrate, chloride, bromide, iodide, lactate, carbonate, phosphate, citrate, pantothenate, tartrate, succinate, malonate, malate, nicotinate, glycerate and gluconate.

Claims 13 and 14 are added.

Introduction

House dust as a mixture of biological materials has been known as a major cause of allergic diseases for more than 70 years [1,2]. IgE sensitization and symptoms of atopic diseases have been attributed to protein components in house dust such as pollen, animal dander, moulds, and domestic mites [1,3-8]. Inorganic compounds and other irritants in dust seem to enhance the sensitization process and the inflammatory skin and mucosa symptoms [9-11].

Over the past few decades epidemiological studies from many industrialized countries have indicated an increasing prevalence of atopic diseases [12-15]. Recent studies have shown that atopic diseases are twice as frequent in the children investigated than in their parents [14,15]. The increasing prevalence may be explained by changes in lifestyle and diet, in addition to exposure to environmental factors [6,7,11-13]. Passive smoking in early infancy, combined with high indoor humidity and environmental allergens, seems to be particularly harmful [9,11].

The present study is concerned with the correlation of allergen amounts in living-rooms and mattresses in homes and classrooms of children living in an arctic area on 70° north and, furthermore, the proportion of major allergens of *Dermatophagoides pteronyssinus* (Der p 1) and *Dermatophagoides farinae* (Der f 1) compared with mite counts in mattresses. Special attention was given to the occurrence of house dust mite (HDM) allergens in homes of HDM-sensitized children. Of particular interest was the presence of other allergens than HDM in schools and homes and their relationship to atopy.

Materials and methods

Dust collection and patients

Dust samples were collected from living-rooms and mattresses in 19 homes of HDM-sensitized children and in 19 homes of non-atopic children as a control group during January and March 1994. The atopic and non-atopic children were matched for age, sex and residential area. All 38 children were selected from 424 schoolchildren aged 7-12 years living in the community of Sør-Varanger, northern Norway, as described in detail previously [15]. Additional dust samples were similarly collected from 14 classrooms in seven schools in the same area. The average outdoor temperature was between -4.5° and -13.5°C and the mean relative humidity between 85 and 90%, corresponding to an absolute outdoor humidity between 1.6 and 2.8 g/kg during the months of investigation (personal communication, Norwegian Meteorological Institute, Oslo, Norway).

In this study atopic children are defined as those having current or past histories of atopy, including atopic dermatitis

(AD) and/or mucous membrane atopy (MMA). Atop dermatitis was defined according to the criteria of Hanif & Rajka [16]. A diagnosis of MMA was confirmed if the child had a history of asthma and/or allergic rhinoconjunctivitis in response to known or strongly suspected allergen [15]. Children with positive skin prick test(s) (SPT) with a clinical history of atopic diseases were defined as later atopics [17].

Completed questionnaires were obtained from all home and schools on the day of the investigation, focusing on type of building, location, number of family members, pet, family smoking habits, carpeted floors, insulation, renovation and the child's living conditions before the age of 7. Special attention was given to the ventilation system, dam patches, e.g. condensation on windows, and previous water leakages.

Absolute indoor humidity (AIH) was calculated from simultaneous measurements of relative humidity and indoor temperature (Mollier diagram) using a calibrated thermohygrometer (Therm 2250-1 No. 887944, Ahlbor Meß- und Regelungstechnik, Holzkirchen, Germany) and a standard swingsychrometer (S. Brannan and Son Ltd Cleator Moor, Cumbria, UK).

Dust samples were collected by vacuuming a 12 m² floor area in living-rooms (centre of the room/TV area) and classrooms for a total of 9 min. Two dust samples were collected from each mattress. Each dust sample was vacuumed from half of the upward facing surface and vertical side of the child's mattress and inside of the bed for a total of 1.5 min. A nozzle (Allergologisk Laboratorium A/S, Hørsholm, Denmark) was connected to the inlet of the suction tube of a household vacuum cleaner (Nilfisk GM 9C Fisker and Nielsen A/S, Copenhagen, Denmark). According to the manufacturer, the nozzle was fitted with a Whatman qualitative filter paper grade 1 (Cat. No. 1001070, Whatman International Ltd, Maidstone, UK) with a diameter of 7.0 cm and with a pore size retaining 97% of particles between 0.1 and 1.0 µm. The nozzle was carefully cleaned and a new filter paper fitted before each sampling. The parents have been instructed not to vacuum mattresses or floors for one week prior to sampling. Each dust sample was sealed in plastic bag and stored at -18°C until preparation. Dust samples were weighed and extracted with 12 ml phosphate buffered saline containing 0.05% Tween 20, pH 7.4, for 24 h at 4°C, with shaking. The extracts were centrifuged at 3000 r.p.m. and 4°C for 30 min. The supernatant fluid was stored at -18°C until analysed.

Human sera

Pooled human sera from patients with Type I allergy were used in the radio-allergen sorbent test (RAST) inhibition and have been described previously [15,18,19].

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アロファン

高アレルギー) 免疫学的機序によっておこる生体の1つの病的過程を指すが定義は必ずしも一致していない。生体内で抗原抗体反応が起きた結果、生じてくる毒性物質や、遊離するヒスタミン様物質またはアセチルコリンなどが生体に影響をおよぼすために起こる反応と考えられている。因とする抗体の性質の違いから即時型と遅延型の2つの型に分けられている。前者は、群(じん)麻疹、喘息、腎炎などのアナフィラキシー反応、後者は細菌感染による感染アレルギー、薬剤などによる接触皮膚炎など、ツベルクリン反応で代表される反応を含んでいる。またこれらの原因となる抗原物質を「アレルゲン」と呼ぶ。

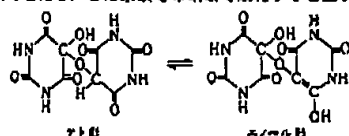
アレルゲン [英 allergen 仏 allergène 独 Allergen 露 аллерген] 「アレルギーの原因となるものを一般にアレルゲンという。大部分はタンパク質系あるいはコリン系の物質である。植物の花粉、カビの胞子などが直接アレルギーの原因になっている場合もある。

アレン [英 allene 仏 allène 独 Allen 露 аллен] [1] $H_2C=C=CH_2$ ジオレフィンに属する。融点 $-146^\circ C$, 沸点 $-32^\circ C$ の気体。ジブロムプロピレンを至終末で脱臭素して得られる。 $H_3C-C(Br)CH_2Br + Zn \rightarrow H_3C-C=CH_2 + ZnBr_2$ 。硫酸の存在で水を付加するとアセトンになる。 $H_2C=C=CH_2 + 2H_2O \rightarrow H_3C-C(OH)_2CH_3 \rightarrow CH_3COCH_3 + H_2O$ 。 [2] 上記アレンの置換体を単にアレンまたはアレン型化合物(allene compound)とよぶことがある。たとえば右の構造のアレンは不斉炭素原子はないが、分子全体として対称性がないために1対の対象体が生じ、光学異性体が分割されている。

アロ異性 [英 alloisomerism 仏 alloisomérie 独 Alloisomerie 露 аллоизомерия] = 立体異性。

アロキサン [英 alloxan 仏 alloxane 独 Alloxan 露 аллоксан] $C_4H_4N_2O_4$ 。メソシュウ酸の環式*ウレイドで、メソオキサリル尿素ともいう。バルビツル酸のオキシ置換体にあたる。尿酸を硝酸で酸化するときアロキサンチンとともに生成し、4水化物の無色の柱状品として得られる。空中で風化して1水化物となり、 $150^\circ C$ 以上で無水物となる。アセトンまたは水酢酸から析出させた無水物(柱状品)は $230^\circ C$ で赤変、融点 $256^\circ C$ (分解)。その水溶液は酸性で皮膚を紫紅色に染める。一連の環式ウレイド誘導体類を合成する母体になる。アロキサンチンのオキシムを*ピコルン酸という。

アロキサンチン [英 alloxanthine 仏 Alloxanthin 露 аллоксантин] $C_6H_4N_2O_8$ 。ふつうのものは3水化物で、無色の柱状品。 $225^\circ C$ で黄変、 $255^\circ C$ で分解。アンモニアにふれると赤変する。アロキサンチンを生じる水素で還元し、また尿酸を希硝酸で酸化すると生ずる。



ケト-エノール互変異性をなす。アルカリの作用によりアロキサンチンとジアルル酸とを、また酸化によってはアロキサンチンを生ずる。

アロケイ皮酸 [英 allocinnamic acid 仏 acide allocinnamique 独 Allozimsäure 露 аллокоричная кислота] → ケイ皮酸。

アロコラン酸 [英 allocholan acid 仏 acide allocholanique 独 Allocholansäure 露 аллохолановая кислота] → コラン酸。

アロース [英 allolose 独 Allolose 露 аллоза] $C_6H_{12}O_6$ 。アルドヘキソースの一種。D-アロースはそのエピマーであるD-アルトロースと $HCOH$ とともにD-リボースの増成によって合成される。 $HCOH$ 融点 $128^\circ C$ (β型)。比旋光度 $[\alpha]_D^{20} = +0.8^\circ$ 。 $HCOH$ + 14.4° 。D-アロースは自然界に存在しないが、 $HCOH$ デオキシ誘導体(ジギトキソースなど)は存在する。

アロステリック酵素 [英 allosteric enzyme 仏 enzyme allostérique 独 allosterische Ferment 露 аллостерический фермент] アロステリックとは「立体的に異なる」という意味である。アロステリック酵素という言葉は次の様に混同して用いられている。1) 基質とは立体構造を異にする物質(これをエフェクターとよぶ)が結合することにより、反応速度が変化する酵素。2) エフェクターの結合により、その立体構造を変化する酵素。この変化に基づいて、基質との親和力が変化する。これ以外に、3) 反応速度を基質の濃度に対してプロットした場合、S字形曲線を与える酵素。すなわち基質の濃度により反応速度が値何現象的に変化する酵素を指すこともある。現在最も広く用いられているのは3)の定義である。酵素によっては1), 2), 3)の定義を同時に満足しているものもあるし、その1つだけに相当するものもある。また1)の定義にしても、反応速度がミハリス定数 K_m の変化の結果生ずるもの、最大値 V_{max} の変化によるもの、両者が混合しているものがある。例えば、トレオニンデアミナーゼの反応速度を基質に対してプロットすればS字形曲線を与える。この場合、ホモトロピックなアロステリック効果とよぶ。これは上の3)の定義によるわけである。上の酵素にさらにイソロイシン(エフェクター)を加えると、S字形曲線の程度がはげしくなり、見かけ上のミハリス定数 K_m は増加する。この場合にはヘトロトロピックなアロステリック効果といい、これは1)の定義に合うアロステリック効果である。アロステリックエフェクターは代謝の最終産物であることが多い。すなわち最終産物の濃度が増加すれば、その酵素の反応速度が減少するから、細胞内の代謝最終産物の濃度を一定に保つように調節していると考えられる。

アロテルル酸 [英 allotelluric acid 仏 acide allotellurique 独 Allotellursäure 露 аллотеллуровая кислота] $(H_2TeO_4)_n$ 。オルトテルル酸 H_6TeO_6 を封管中 $140^\circ C$ で融解して得られる無色粘着性のあるシロップ状物質。構造的にはポリメタテルル酸であるとされる。水と任意の割合に混ざり、酸性はオルトテルル酸より大きい。水溶液を放置すれば徐々にオルトテルル酸になる。

アロファン酸 [英 allophanic acid 仏 acide allophanique 独 Allophansäure 露 аллофановая кислота] $H_2NCONHCOOH$ 。炭酸のモノウレイドに相当するが、遊離酸は知られていない。エステル $H_2NCONHCOOR$ (R はアルキル基など)は尿素にクロルギ酸エ

Allergen: The source causing allergy is called as allergen in general. Most are substances relating to protein or choline. Plant pollen or fungus spore happens to be the source of allergy directly.